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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/803,918	DAYER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) *1-8,11-14,18-35,44,45 and 50-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-10, 15-17, 36-43 and 46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-61 are pending.

2. Claims 1-8, 11-14, 18-35, 44-45, and 50-61 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Applicant is advised that should claim 9 be found allowable, claim 10 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

4. In view of the amendment filed 4/16/03, the following rejections remain.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 9-10, 15-17, 36-43 and 46-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated apo-A-1 fragment T-cell activation inhbitor-like polypeptide fragment produced by a process comprising culturing an eukaryotic cell comprising a vector comprising a nucleic acid molecule consisting essentially of a nucleotide sequence selected from: the nucleotide sequence as set forth 9(a) through (h), and (j), wherein a culture condition suitable for expression said polypeptide, 16 a(2) through (8) 16b (2) through (9), (2) an isolated apo-A-1 fragment T cell activation inhibitor like polypeptide fragment consisting of consisting essentially of an amino acid sequence selected from: 15 (a) through (f), (3) a composition comprising said polypeptide fragment, and a pharmaceutically acceptable carrier, (4) a fusion polypeptide comprising the polypeptide mentioned above and an IgG constant domain for inhibiting the production of IL-1 and TNF alpha in vitro in THP-1 cells activated by membranes of stimulated HUT-78 cells, **does not** reasonably provide enablement for (1) *any* apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment produced by a process

culturing a eukaryotic cell comprising a vector comprising a nucleic acid molecule consisting essentially of any nucleotide sequence selected from any nucleotide sequence which hybridizes under "moderately or highly stringent conditions" to the complement of at least one of claim 9 (a) to (h), wherein the encoded polypeptide has any activity of the polypeptide as set forth in SEQ ID NO: 2; any nucleotide sequence that is at least about 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99 percent identical to at least one of (a)-(j), wherein the encoded polypeptide has any activity of the polypeptide as set forth in SEQ ID NO: 2; any nucleotide sequence encoding any allelic variant or splice variant of the nucleotide sequence according to at least one of claim 9(a)-(j) wherein the encoded polypeptide has any activity of the polypeptide as set forth in SEQ ID NO: 2; any nucleotide sequence selected from at least one of claim 9(k), (l), and (m) comprising any fragment of at least about 16 nucleotides, (2) *any* isolated apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment consisting essentially of an amino acid sequence such as an amino acid sequence that is at least about 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99 percent identical to the amino acid sequence of at least of 15(a), (b) or (c) wherein the encoded polypeptide has any activity of the polypeptide as set forth in SEQ ID NO: 2; any fragment of the amino acid sequence set forth in claims 15(a), (b), (c), (d), or (e) comprising at least 25 amino acids residues, wherein the encoded polypeptide has any activity of the polypeptide as set forth in SEQ ID NO: 2; any allelic variant or splice variant of amino acid sequence in claims 15(a)-(f) wherein the encoded polypeptide has any activity of the polypeptide as set forth in SEQ ID NO: 2; (3) any isolated apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment as set forth in claim 16, (4) any composition comprising any polypeptide fragment mentioned above and a pharmaceutically acceptable formulation agent, (5) any fusion polypeptide comprising any isolated apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment mentioned above and any heterologous amino acid sequence, any heterologous sequence is an IgG constant domain or any fragment thereof for treating any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims for the same reasons set forth in Paper No 13.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working

examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only human Apo-A-1 of SEQ ID NO: 2 encoding by the polynucleotide of SEQ ID NO: 1. The full length human Apo-A1 inhibits the production of TNF-α and IL-1β in vitro in THP-1 cells activated by membranes of stimulated HUT-078 cells or antigen-activated peripheral blood monocyte (PBMC) in vitro (See Figures 6-11, page 100). The specification further discloses the inhibitory activity of Apo A-1 corresponds to the fraction on the Western Blot having a molecular weight of 28,000 ± 10,000 (Fig 6D, page 99 of specification).

With the exception of the full length polypeptide of SEQ ID NO: 2 for inhibiting the production of TNF-α and IL-1β in vitro, the specification does not teach how to make and use *any* polypeptide mentioned above for treating any disease. The term "consisting essentially of" is open-ended. It expands the polypeptide fragment to include additional amino acid residues at either or both ends and the corresponding nucleotide sequence encoding the additional amino acids at either or both ends. The state of the art recognizes that sequence identity does not predict biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama *et al* teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al.* teach further that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet *et al* teach that a single Glu to Val substitution in the subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, paragraph bridging columns in particular). Given the indefinite number of undisclosed polypeptide and the corresponding nucleotides for the additional amino acids, there is insufficient guidance as to the specific amino acids should be added, and whether the resulting polypeptide after modification

will still retain the structural and functional properties as SEQ ID NO: 2, in turn, suitable for pharmaceutical use. As such, further research would be required to identify the fragment having the specific activity as the full length polypeptide of SEQ ID NO: 2, in turn, for treating a specific disease.

Further, there is insufficient working examples of any fragment has any activity, much less treating any disease using any fragment such as the ones recited in claims 9-10, 15-17. Even if the polypeptide is full length, there is no in vivo working example that the claimed polypeptide can treat any disease. A pharmaceutical composition in the absence of in vivo data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

With regard to polypeptide produced by the nucleic acid molecule consisting essentially of *any* nucleotide sequence which hybridizes under "moderately or highly stringent conditions" to the complement of *any* nucleotide sequence such as the ones recited (a) to (F) of claim 1 wherein the encoded polypeptide has *any* activity of the polypeptide as set forth in SEQ I DNO: 2, or *any* nucleotide sequence complementary to the nucleic acid molecule consisting essentially of *any* nucleotide sequence which "hybridizes under moderately or highly stringent conditions" to the complement of any nucleotide sequence of (a) to (F) wherein the encoded polypeptide has any activity of the polypeptide as set forth in SEQ I DNO: 2, the specification does not disclose the specific conditions used by applicants such as salt concentration, melting and annealing temperature and the duration of hybridization for the specific polynucleotide encoding the specific polypeptide. The state of the prior art as exemplified by Wallace *et al* is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Furthermore, a database search was done for 20mers of the specified sequence, the total number of hits was 143,797,728 which suggest that some of the polynucleotides encompassed by the claims would not preferentially hybridize to SEQ ID NO: 1. Further, the term "consisting essentially of" is open-ended. It

expands the polypeptide, the corresponding polynucleotide to include additional nucleotide at either or both ends. Given the number of undisclosed polynucleotide, it is unpredictable which undisclosed polynucleotide would hybridize specifically to a polynucleotide encoding a polypeptide having additional undisclosed amino acids, much less having a specific activity such as inhibition of TNFα and IL-1β production, in turn, would be useful for treating any disease.

With regard to claim 10 which recites a polypeptide produced by a polynucleotide sequence consisting of a nucleotide sequence that is at least "about 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical to the nucleotide sequence such as the ones recited in claim 1, wherein the polynucleotide sequence has any activity as set forth in SEQ ID NO: 2, the specification discloses only human Apo A-1 comprising SEQ ID NO: 2 encoded by of a polynucleotide of SEQ ID NO: 1 and a fragment of human Apo A-1 encoded by polynucleotide sequence consisting of SEQ ID NO: 4. The specification does not disclose any polypeptide encoding by a polynucleotide sequence consisting of a nucleotide sequence that is at least "about 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical to the nucleotide sequence, much less demonstrating having any activity. Attwood *et al* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable. Thus, knowing structure alone will not inherently tell us function (See figure, entire document). Given the indefinite number of polypeptide with undisclosed functions, it follows that any polypeptide for inhibiting the production of IL-1 TNFα and IL-1β is not enabled.

With regard to polypeptide produced by polynucleotide encoding an "allelic variant" or "splice variant" of any polynucleotide according to claim 1, the specification discloses only human Apo A-1 comprising SEQ ID NO: 2 encoded by a polynucleotide of SEQ ID NO: 1 and a fragment of human Apo A-1 encoded by polynucleotide sequence consisting of SEQ ID NO: 4. The specification defines "AFTI polypeptide allelic variant" on page 14 as several or many possible naturally occurring alternative forms of a gene occupying a given locus on a chromosome of any organisms or a population of organisms. There is insufficient guidance and working example demonstrating any "allelic variant" or "splice variant" having the same activity as the claimed polypeptide of SEQ ID NO: 2, much less treating any disease.

With regard to a polypeptide produced by polynucleotide such as the ones recited in claim 2(d) "comprising" a fragment of at least about 16 nucleotides, the term "comprising" is open-ended. It expands the nucleotide to include additional nucleotide to either or both ends of

polynucleotide. There is insufficient guidance and working example demonstrating any undisclosed polypeptide encoding by any undisclosed polynucleotide having additional nucleotide would have the same structure and functions as polypeptide of SEQ ID NO: 2. Even if the polypeptide encoding by the polynucleotide is limited to 16 nucleotides, there is insufficient guidance which fragment within the full length of polynucleotide encoding the fragment of polypeptide of SEQ ID NO: 2 would have the same activity as the full length polypeptide of SEQ ID NO: 2. Further, a 16 polynucleotides encoded a polypeptide of only four amino acids in length, there is no working example demonstrating any polypeptide having only 4 amino acids in length has any activity as the claimed polypeptide of SEQ ID NO: 2 such as inhibiting the production of IL-1 TNFα and IL-1β in vitro. Since the polypeptide encoding by the polynucleotide mentioned above is not enabled, it follows that any nucleotide sequence complement to any undisclosed nucleotide mentioned above is not enabled.

With regard to "ortholog" of SEQ ID NO: 2 having an activity of the polypeptide of SEQ ID NO: 2, the specification on page 15 defines "ortholog" as any polypeptide from another species that corresponds to an AFTI polypeptide of SEQ ID NO: 2. The specification discloses only human AFTI of SEQ ID NO: 2. There is no other polypeptide in the specification that is an ortholog of human Apo A-I, let alone having the same activity such as the claimed polypeptide of SEQ ID NO: 2. Given the indefinite number of undisclosed ortholog of SEQ ID NO: 2 from any other species, it is unpredictable which undisclosed amino acid sequence of any ortholog of SEQ ID NO: 2 will have the same structure, much less the activity as SEQ ID NO: 2, in turn, would be useful for any purpose.

With regard to an isolated polypeptide "consisting essentially of" an amino acid sequence that is at least about "about 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO: 2, residues 25 to 144 of SEQ ID NO: 2, or residues 156 to 267 of SEQ ID NO: 2, wherein the polypeptide sequence has any activity as set forth in SEQ ID NO: 2, the specification discloses only human Apo A-1 comprising SEQ ID NO: 2 that inhibits the production of TNFα and IL-1β. The specification does not teach any other polypeptide having any sequence identity with SEQ ID NO: 2, let alone having the same function as the claimed sequence of SEQ ID NO: 2. Further, the term "consisting essentially of" is open-ended. It expands the polypeptide to include additional amino acid residues at either or both ends in addition to having various percent identities. Given the indefinite undisclosed polypeptide, it is unpredictable which undisclosed polypeptide would have

the same functions as polypeptide of SEQ ID NO: 2. Although sequence alignment using various computer program such as the ones recited in claim 17 is known in the art, sequence identity is not equal having the same function.

Attwood *et al* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable. Thus, knowing structure alone will not inherently tell us function (See figure, entire document). Given the functions of any polypeptide mentioned above, it follows that any polypeptide for inhibiting the production of IL-1 TNFα and IL-1β is not enabled. The specification does not disclose whether any allelic variant have the same activity much less having the same structure. Since the allelic variant and splice variant are not enabled, it follows that any fragment of any disclosed allelic variant and splice variant are not enabled

With regard to fragment "comprising" at least about 25 amino acid residues as recited in claim 15 (h), the term "comprising" is open-ended. It expands the fragment to include additional undisclosed amino acid residues at either or both ends in addition to residues 25 to 194 of SEQ ID NO: 2, residues 25 to 144 of SEQ ID NO: 2, or residues 156 to 267 of SEQ ID NO: 2 which already recited in the claim. There is insufficient guidance as the specific amino acids that can be added or modified such that after addition would retain structure and activity as SEQ ID NO: 2. There is no working example demonstrating any fragment has any activity. Not only the amino acid sequence that is an ortholog of SEQ ID NO: 2 not disclosed, it is unpredictable which fragment "comprising" the undisclosed ortholog of SEQ ID NO: 2 would have the same activity as SEQ ID NO: 2. Likewise, there is insufficient guidance and working example demonstrating any fragment of any amino acid sequence that is about 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO: 2, residues 25 to 144 of SEQ ID NO: 2, or residues 156 to 267 of SEQ ID NO: 2 having the same activity as SEQ ID NO: 2. Since the polypeptides are not enabled, it follows that polypeptides covalently modified with any water-soluble polymer such as the ones recited in claims 41 and 43 are not enabled. It also follows that any composition comprising any undisclosed polypeptide are not enabled. It also follows that any fusion polypeptide comprising any undisclosed amino acid sequence mentioned above and any heterologous amino acid sequence is not enabled. Further, the term "heterologous amino acid sequence" could be any undisclosed sequence. Given the indefinite number of undisclosed "heterologous amino acid sequence", it is unpredictable which

fusion protein comprising any undisclosed "heterologous amino acid sequence" and polypeptide such as the ones recited in claim 15 would have the same function as SEQ ID NO: 2, in turn, would be useful for any purpose.

For these reasons, it would require undue experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 4/16/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the properties of apo A-1 were well known at the time the earliest priority document was filed March 13, 2000, (2) A search of Genback database for "aoplipoprotein A-1" returned 452 protein and 1484 nucleotides sequences from a wide variety of species. (3) Artisans in this area are highly skilled and often have doctoral degrees. (4) The phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps and those and those that do not materially affect the basic and novel characteristics of the claimed invention. (5) The claims do not require that any amino acids should be added to the AFTI polypeptide fragments. Instead, the claims recite particular AFTI polypeptide fragments (and homologous sequences) which may also contain additional amino acids so long as those amino acids do not "materially affect the basic and novel characteristics of the claimed polypeptides. (6) None of the rejected claims specifically recites a pharmaceutical uses. The specification discloses multiple uses of AFTI polypeptide fragments, including, for example, use as antigens (page 15, lines 12-15). (7) Pages 21-23 of the specification provide a detailed description of hybridization conditions that are "highly" or "moderately" stringent. (8) The claims require not only that a nucleic acid hybridize with the complement of a specific sequence, but also that they have encode a polypeptide with an activity of SEQ ID NO: 2. (9) Although the specification discloses only human apo A-1 sequences, Applicants are not required to disclose that which is well known in the art. (10) The Office asserts that the specification does not enable one skilled in the art to make

and use a polypeptide produced from a polynucleotide consisting essentially of a nucleotide sequence according to claim 2 wherein the polynucleotide comprises a fragment of at least 16 nucleotides or a polynucleotide encoding a polypeptide of at least 25 amino acid residue. According to the Office, the term "comprising" renders the polynucleotide open-ended. However, the claimed polypeptides are produced using nucleotide sequences consisting essentially of the sequences recited by claim. The recited sequence comprises smaller sequences does not render them open-ended. The metes and bounds are still set by SEQ ID NO: 1 and 2 and those amino acids that do not materially affect the basic and novel characteristics of the claimed polypeptides.

In response to Applicants' argument that the claims recite particular AFTI polypeptide fragments (and homologous sequences) which may also contain additional amino acids so long as those amino acids do not "materially affect the basic and novel characteristics of the claimed polypeptides", it is noted that the specific activity of SEQ ID NO: 2 is not defined in any of the claims. Even if a search of Genback database for "aoplipoprotein A-1" returned 452 protein and 1484 nucleotides sequences from a wide variety of species, it is unpredictable which fragment has the undisclosed activity of the polypeptide of SEQ ID NO: 2. It is not routine for one skill in the art to screen databases for polypeptide fragment for unspecified activity.

As to Apo-A-1 fragment produced by a nucleotide sequence which hybridizes under moderately or highly stringent conditions, the specific moderately or the specific highly stringent conditions used by Applicants such as the ones disclose on page 21-23 are not recite in the claims.

As to Apo-A-1 fragment produced by a nucleotide sequence that is at least bout 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical to the specific nucleotide sequence encoding the specific polypeptide residues wherein the nucleotide sequence encodes a polypeptide that has any activity of SEQ ID NO: 2, again the specific activity is not recited in any of the claims. Further, the specification on page 16 defines AFTI polypeptide variants are AFTI polypeptide comprising amino acid sequences having one or more amino acid sequence substitutions, deletions, additions ...the variants have from 1 to 3 or more than 100 amino acid substitutions, insertions, additions and/or deletions. Furthermore, there is no guidance in the specification as to which amino acids within the amino acid sequence (polypeptide) of SEQ ID NO: 2, the corresponding polynucleotide can be substitute, added or deleted and whether the resulting polypeptide would retain the structure and function as SEQ ID NO: 2. Attwood *et al* teach that protein

function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable. Thus, knowing structure alone will not inherently tell us function (See figure, entire document). Since the Apo-A1 fragments produced by the a nucleotide sequence that is at least bout 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical to the specific nucleotide sequence encoding the specific polypeptide residues wherein the nucleotide sequence encodes a polypeptide that has any activity of SEQ ID NO: 2 are not enabled, it follows that Apo-A1 fragments covalently modified with any water-soluble polymer such as the ones recited in claims 41 and 43 are not enabled. It also follows that any composition comprising any undisclosed polypeptide are not enabled. It also follows that any fusion polypeptide comprising any undisclosed amino acid sequence mentioned above and any heterologous amino acid sequence is not enabled. Further, the term "heterologous amino acid sequence" could be any undisclosed sequence. Given the indefinite number of undisclosed "heterologous amino acid sequence", it is unpredictable which fusion protein comprising any undisclosed "heterologous amino acid sequence" and polypeptide such as the ones recited in claim 15 would have the same function as SEQ ID NO: 2, in turn, would be useful for any purpose.

7. Claims 9-10, 15-17, 36-43 and 46-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention for the same reasons set forth in Paper No 13.

The specification does not reasonably provide a **written description** of (1) *any* apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment produced by a process culturing a eukaryotic cell comprising a vector comprising a nucleic acid molecule consisting essentially of any nucleotide sequence selected from any nucleotide sequence which hybridizes under "moderately or highly stringent conditions" to the complement of at least one of claim 9 (a) to (h), wherein the encoded polypeptide has any activity of the polypeptide as set forth in SEQ ID NO: 2; any nucleotide sequence that is at least about 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99 percent identical to at least one of (a)-(j), wherein the encoded polypeptide has any activity of the polypeptide as set forth in SEQ ID NO: 2; any nucleotide sequence encoding any allelic variant or splice variant of the nucleotide sequence according to at least one of claim 9(a)-(j) wherein the encoded polypeptide has any activity of the polypeptide as set forth in SEQ ID NO: 2; any

nucleotide sequence selected from at least one of claim 9(k), (l), and (m) comprising any fragment of at least about 16 nucleotides, (2) *any* isolated apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment consisting essentially of an amino acid sequence such as an amino acid sequence that is at least about 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99 percent identical to the amino acid sequence of at least of 15(a), (b) or (c) wherein the encoded polypeptide has any activity of the polypeptide as set forth in SEQ ID NO: 2; any fragment of the amino acid sequence set forth in claims 15(a), (b), (c), (d), or (e) comprising at least 25 amino acids residues, wherein the encoded polypeptide has any activity of the polypeptide as set forth in SEQ ID NO: 2; any allelic variant or splice variant of amino acid sequence in claims 15(a)-(f) wherein the encoded polypeptide has any activity of the polypeptide as set forth in SEQ ID NO: 2; (3) any isolated apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment as set forth in claim 16, (4) any composition comprising any polypeptide fragment mentioned above and a pharmaceutically acceptable formulation agent, (5) any fusion polypeptide comprising any isolated apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment mentioned above and any heterologous amino acid sequence, any heterologous sequence is an IgG constant domain or any fragment thereof for treating any disease.

The specification discloses only human Apo-A-1 of SEQ ID NO: 2 encoding by the polynucleotide of SEQ ID NO: 1. The specification further discloses the full length human Apo-A1 inhibits the production of TNF-α and IL-1β in vitro in THP-1 cells activated by membranes of stimulated HUT-078 cells or antigen-activated peripheral blood monocyte (PBMC) in vitro (See Figures 6-11, page 100). The specification discloses the inhibitory activity of Apo A-1 corresponds to the fraction on the Western Blot having a molecular weight of 28,000 ± 10,000 (Fig 6D, page 99 of specification).

With the exception of the specific polypeptide mentioned above for inhibiting the production of TNF-α and IL-1β in vitro, there is insufficient written description about the structure associated with function of *any* isolated polypeptide "consisting essentially" of *any* amino acid sequence selected from: (a) an amino acids sequence as set forth in residues 25 to 194 of SEQ ID NO: 2; (b) residues 25 to 144 of SEQ ID NO: 2; (c) residues 156 to 267 of SEQ ID NO: 2; (d) residues 25 to 113 of SEQ ID NO: 2; (e) residues 73 to 113 of SEQ ID NO: 2; (f) *any* "ortholog" of SEQ ID NO: 2, *any* amino acid sequence that is at least "about 70, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical to any amino acid sequence mentioned in (a), (b) or (c) mentioned above. The term "consisting essentially of" or "comprising" is open-ended. It

expands the polypeptide to include additional amino acids at either or both ends, and the corresponding polynucleotide encoding the additional amino acids.

Further, the specification discloses only human Apo A-1 of SEQ ID NO: 2 that inhibit the production of TNF-α and IL-1β in vitro. Given the lack of a written description of *any* additional representative species of polypeptide of Apo A-1, *any* ortholog of SEQ ID NO: 2, *any* amino acid sequence that is at least "about 70, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical" to *any* amino acid sequence mentioned in (a), (b) or (c) mentioned above and *any* polypeptide produced by *any* polynucleotide encoding said polypeptides, *any* fusion polypeptide, *any* composition comprising *any* polypeptide mentioned above for treating any disease, *any* polypeptide modified with *any* water-soluble polymer, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 4/16/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) Applicants have explicitly described three nucleic acid sequences nucleotides 73 to 601, 73 to 451 and 485 to 820 in SEQ ID NO: 1 and five amino acid sequences (residues 25 to 194, 25 to 144, 25 to 113, 73 to 113 and 156 to 267 of SEQ ID NO: 2 that encode or are AFTI polypeptide fragments according to the claimed invention. (2) Applicants have described in great detail hybridization conditions and preferred amino acid substitutions that identify homologous or related sequences that are also part of their invention.

However, the three nucleic acid sequences nucleotides 73 to 601, 73 to 451 and 485 to 820 in SEQ ID NO: 1 and the five amino acid sequences (residues 25 to 194, 25 to 144, 25 to 113, 73 to 113 and 156 to 267 of SEQ ID NO: 2 are all from human, which is one species in a genus. With regard to hybridization, the specific moderately or the specific highly stringent conditions used by Applicants such as the ones disclose on page 21-23 are not recite in the claims. As to the preferred amino acid substitutions that identify homologous or related sequences, the specification on page 16 defines AFTI polypeptide variants are AFTI polypeptide comprising amino acid sequences having one or more amino acid sequence substitutions,

deletions, additions ...the variants have from 1 to 3 or more than 100 amino acid substitutions, insertions, additions and/or deletions. There is insufficient written description about which amino acids within the amino acid sequence (polypeptide) of SEQ ID NO: 2, and the corresponding polynucleotide can be substitute, added or deleted and whether the resulting polypeptide would retain the structure and function as SEQ ID NO: 2. Given the indefinite number of undisclosed apo-A-1 fragment produced or encoded by any nucleotide sequence that is at least bout 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical to the specific nucleotide sequence encoding the specific polypeptide residues wherein the nucleotide sequence encodes a polypeptide that has any activity of SEQ ID NO: 2, the undisclosed apo-A fragment such as the allelic variant, or splice variant or any nucleotide sequence that is at least bout 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical to SEQ ID NO: 2 is not adequately described. Given the lack of additional Apo-A-1 fragment from other species, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 15 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,408,038 (April 1995, PTO 892).

The '038 patent teaches a fusion polypeptide such as A-I/B-100 comprising the polypeptide fragment consisting of amino acid sequence from about residue 19 to 240 of SEQ ID NO: 3 fused to a heterologous sequence such as the reference SEQ ID NO: 1 (Apo B-100) (See claims 10-12 of '038 patent, in particular). The reference SEQ ID NO: 3 is 100% identical to the claimed SEQ ID NO: 2. The '038 patent teaches the entire reference apo A-I amino acid sequence or a fragment of the reference apo A-I, can be fused to apo B-100 (See column 16, lines 7, in particular). The term "consisting essentially of" expands the claimed amino acid sequence residues 25 to 194 of SEQ ID NO: 2 to read on the reference residues 19 to 240 of the reference SEQ ID NO: 3. The reference polypeptide fragment comprises at least 25 amino acid residues of the claimed residue 25 to 194 of the claimed SEQ ID NO: 2 since 240 minus 19 is 221 amino

acids, which is at least 25 amino acids. Further, the term "comprises" is open-ended. It expands the fragment to include additional amino acids at either or both ends. The reference polypeptide of SEQ ID NO: 3 inherently has the same activity as the claimed SEQ ID NO: 2 since it is identical to the claimed SEQ ID NO: 2 and the specific activity is not recited in the claim. Further, the term "about" expands the claimed identity to read on the identity of the reference polypeptide fragment. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 4/16/03 have been fully considered but are not found persuasive.

Applicants' position is that the Office relies on the incorrect assertion that the transitional term "consisting essential of" expands the claims to encompass the fusion proteins of the '038 patent. However, the office has provide no basis on which one could reasonably conclude that preparing fusion proteins comprising significant portions of both apo A-1 and apo B does not materially affect the basic and novel characteristics of Applicants' AFTI polypeptide fragments.

However, none of the claims recite a specific activity. Further, the term "heterologous amino acid sequence" in claim 46 encompasses any sequence in the fusion protein.

The '038 patent teaches a fusion polypeptide such as A-I/B-100 comprising the polypeptide fragment consisting of amino acid sequence from about residue 19 to 240 of SEQ ID NO: 3 fused to a heterologous sequence such as the reference SEQ ID NO: 1 (Apo B-100) (See claims 10-12 of '038 patent, in particular). The reference SEQ ID NO: 3 is 100% identical to the claimed SEQ ID NO: 2. The '038 patent teaches the entire reference apo A-I amino acid sequence or a fragment of the reference apo A-I, can be fused to apo B-100 (See column 16, lines 7, in particular). The term "consisting essentially of" expands the claimed amino acid sequence residues 25 to 194 of SEQ ID NO: 2 to read on the reference residues 19 to 240 of the reference SEQ ID NO: 3. The reference polypeptide fragment comprises at least 25 amino acid residues of the claimed residue 25 to 194 of the claimed SEQ ID NO: 2 since 240 minus 19 is 221 amino acids, which is at least 25 amino acids. Further, the term "comprises" is open-ended. It expands the fragment to include additional amino acids at either or both ends. The reference polypeptide of SEQ ID NO: 3 inherently has the same activity as the claimed SEQ ID NO: 2 since it is identical to the claimed SEQ ID NO: 2 and the specific activity is not recited in the claim. Further, the term "about" expands the claimed identity to read on the identity of the reference polypeptide fragment.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 15, 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,408,038 (April 1995, PTO 892) in view of US Pat 5,116,964 (May 1992; PTO 892).

The teachings of the '038 patent have been discussed supra. The '038 patent further teaches apoA-I is unstable (see column 2, lines 6-8, in particular).

The claimed invention as recited in claim 47 differs from the reference only that the fusion polypeptide wherein the heterologous amino acid sequence is an IgG constant or fragment thereof.

The '964 patent teaches immunoglobulin fusion polypeptide such as CH2 and CH3 domains of the constant region of an immunoglobulin or fragment thereof fused to any polypeptide of interest such as LHR (See abstract, column 10, lines 10-16, in particular). The advantage of immunoglobulin fusion polypeptide extends the half-lives of the fusion protein and useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the LHR of the immunoglobulin fusion polypeptide as taught by the '964 patent or the B-100 polypeptide in the A-I/B-100 fusion protein as taught by the '038 patent for a fusion protein comprising apo A-I fused to IgG constant or fragment thereof as taught by the '038 patent and the '964 patent. From the combined teachings of the references, it is

apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '038 patent teaches apoA-I is unstable (see column 2, lines 6-8, in particular). The '964 patent teaches immunoglobulin fusion polypeptide extends the half-lives of the fusion protein and useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular).

Applicants' position is that the Office relies on the incorrect assertion that the transitional term "consisting essential of" expands the claims to encompass the fusion proteins of the '038 patent. However, the office has provide no basis on which one could reasonably conclude that preparing fusion proteins comprising significant portions of both apo A-1 and apo B does not materially affect the basic and novel characteristics of Applicants' AFTI polypeptide fragments. The addition of either '964 patent or the '784 patent does not correct this deficiency, regardless of what those references teach concerning fusion proteins or water-soluble polymers.

However, none of the claims recite a specific activity. Further, the term "heterologous amino acid sequence" in claim 46 encompasses any sequence in the fusion protein.

The '038 patent teaches a fusion polypeptide such as A-I/B-100 comprising the polypeptide fragment consisting of amino acid sequence from about residue 19 to 240 of SEQ ID NO: 3 fused to a heterologous sequence such as the reference SEQ ID NO: 1 (Apo B-100) (See claims 10-12 of '038 patent, in particular). The reference SEQ ID NO: 3 is 100% identical to the claimed SEQ ID NO: 2. The '038 patent teaches the entire reference apo A-I amino acid sequence or a fragment of the reference apo A-I, can be fused to apo B-100 (See column 16, lines 7, in particular). The term "consisting essentially of" expands the claimed amino acid sequence residues 25 to 194 of SEQ ID NO: 2 to read on the reference residues 19 to 240 of the reference SEQ ID NO: 3. The reference polypeptide fragment comprises at least 25 amino acid residues of the claimed residue 25 to 194 of the claimed SEQ ID NO: 2 since 240 minus 19 is 221 amino acids, which is at least 25 amino acids. Further, the term "comprises" is open-ended. It expands the fragment to include additional amino acids at either or both ends. The reference polypeptide of SEQ ID NO: 3 inherently has the same activity as the claimed SEQ ID NO: 2 since it is identical to the claimed SEQ ID NO: 2 and the specific activity is not recited in the claim. Further, the term "about" expands the claimed identity to read on the identity of the reference polypeptide fragment.

13. Claims 15, 36, 38, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,408,038 (April 1995, PTO 892) in view of US Pat No. 5,824,784 (Oct 1998; PTO 892).

The teachings of the '038 patent have been discussed supra.

The claimed invention in claim 38 differs from the reference only that composition wherein the pharmaceutically acceptable formulation agent comprises at least one of a carrier, adjuvant, solubilizer, stabilizer or anti-oxidant.

The claimed invention as recited in claim 40 differs from the reference only that polypeptide is covalently modified with a water-soluble polymer.

The claimed invention as recited in claim 41 differs from the reference only that polypeptide is covalently modified with a water soluble polymer wherein the water soluble polymer is selected from polyethylene glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol.

The '784 patent teaches method and composition for covalently modified any polypeptide of interest such as G-CSF or INF with a water-soluble polymer such as polyethylene glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol (See abstract, column 6, lines 32-67 bridging column 7, lines 1-5, column 9, lines 64-66, in particular). The '1784 patent further teaches pharmaceutically acceptable formulation agent such as carrier such as phosphate buffer, adjuvant, solubilizer such as Tween 80, anti-oxidants such as ascorbic acid, and sodium metafisulfate (See column 11, lines 11-32, in particular). The '784 patent teaches the advantages of N-terminally pegsylated protein provides a homogeneous preparation to ease in clinical application in predictability of lot to lot pharmacokinetics, for desired dosage, increasing circulation time such as sustained release and resistance to proteolysis and other consideration such as lack of antigenicity (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently modified the A-I/B-100 fusion protein as taught by the '038 patent using water soluble polymer as taught by the '784 patent for a water-soluble polymer modified A-I/B-100 as taught by the '038 patent and the '784 patent. From the combined

teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '038 patent teaches apoA-I is unstable (see column 2, lines 6-8, in particular). The '784 patent teaches the advantages of N-terminally pegylated protein provides a homogeneous preparation to ease in clinical application in predictability of lot to lot pharmacokinetics, for desired dosage, increasing circulation time such as sustained release and resistance to proteolysis and other consideration such as lack of antigenicity (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular).

Applicants' position is that the Office relies on the incorrect assertion that the transitional term "consisting essential of" expands the claims to encompass the fusion proteins of the '038 patent. However, the office has provide no basis on which one could reasonably conclude that preparing fusion proteins comprising significant portions of both apo A-1 and apo B does not materially affect the basic and novel characteristics of Applicants' AFTI polypeptide fragments. The addition of either '964 patent or the '784 patent does not correct this deficiency, regardless of what those references teach concerning fusion proteins or water-soluble polymers.

However, none of the claims recite a specific activity. Further, the term "heterologous amino acid sequence" in claim 46 encompasses any sequence in the fusion protein.

The '038 patent teaches a fusion polypeptide such as A-I/B-100 comprising the polypeptide fragment consisting of amino acid sequence from about residue 19 to 240 of SEQ ID NO: 3 fused to a heterologous sequence such as the reference SEQ ID NO: 1 (Apo B-100) (See claims 10-12 of '038 patent, in particular). The reference SEQ ID NO: 3 is 100% identical to the claimed SEQ ID NO: 2. The '038 patent teaches the entire reference apo A-I amino acid sequence or a fragment of the reference apo A-I, can be fused to apo B-100 (See column 16, lines 7, in particular). The term "consisting essentially of" expands the claimed amino acid sequence residues 25 to 194 of SEQ ID NO: 2 to read on the reference residues 19 to 240 of the reference SEQ ID NO: 3. The reference polypeptide fragment comprises at least 25 amino acid residues of the claimed residue 25 to 194 of the claimed SEQ ID NO: 2 since 240 minus 19 is 221 amino acids, which is at least 25 amino acids. Further, the term "comprises" is open-ended. It expands the fragment to include additional amino acids at either or both ends. The reference polypeptide of SEQ ID NO: 3 inherently has the same activity as the claimed SEQ ID NO: 2 since it is identical to the claimed SEQ ID NO: 2 and the specific activity is not recited in the claim.

Further, the term "about" expands the claimed identity to read on the identity of the reference polypeptide fragment.

14. The following new ground of rejection is necessitated by the amendment filed 4/16/03.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

16. Claims 9, 10, 15, 16, 36-43 and 46-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 9-10 and 15-16 recites the broad recitation "nucleotide sequence selected from at least comprising one of (k), (l) and (m) *comprising* a fragment at least about 16 nucleotides", and the claim also recites "nucleotide sequence *consisting essentially of* a nucleotide sequence selected from the nucleotide sequence (k), (l) and (m)" which is the narrower statement of the range/limitation.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

19. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
June 30, 2003

Christina Chan
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